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(54) Title: COMPOSITIONS FOR ENHANCED ACARICIDAL ACTIVITY

(57) Abstract: A composition for control of parasitic insects and acarids, comprising a combination of pyrethroids and chloronicotinyl compounds.

SUMMARY OF THE INVENTION

In accordance with the foregoing, the present invention encompasses a composition for controlling parasitic insects and acarids containing a combination of active ingredients comprising pyrethroids and nicotinyl compounds. The composition is particularly suitable for dermal control of parasitic acarids and insects, particularly ticks, mites and fleas on mammals, as well, as premise control of fleas, ticks and mites and other susceptible insects. By the term " control" or "controlling" herein is meant rendering the insects and acarids innocuous, preferably by killing the insect and acarids to the extent that at least 80% die within days, and preferably within 2 days of application. In the preferred embodiment, the treated target is infested with insects and/or acarids. By the term combination is meant a regimen of applying the two active ingredients, either together or separately but concurrently.

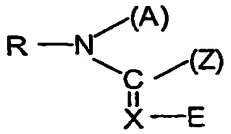
In the presently preferred embodiment, the invention encompasses a composition comprising a combination of permethrin and imidacloprid. It has been found that the combination of these active ingredients produces a synergistic effect of significantly enhancing onset of activity (control) against acarids such as ticks and mites, and long-term activity (control) against ticks and fleas. This is rather unexpected because imidacloprid or permethrin alone generally has limited activity against acarids such as ticks and mites, and permethrin alone, generally, has limited and short duration of activity against fleas. Surprisingly, imidacloprid in combination with permethrin has been found to significantly enhance the kill activity against these parasites, and thus provides excellent control. Moreover, in the use of the combination against fleas, imidacloprid activity has not been negatively affected by the permethrin. The invention is described more fully hereunder.

DETAILED DESCRIPTION OF THE INVENTION

As set forth above, the invention relates to a composition comprising a combination of pyrethroids and chloronicotinyl compounds in effective concentrations to provide enhanced acaricidal activity without

Chloronicotinyl compounds are known, for example, from European Offenlegungsschriften (European Published Applications) Nos. 580 553, 464 830, 428 941, 425 978, 386 565, 383 091, 375 907, 364 844, 315 826, 259 738, 254 859, 235 725, 212 600, 192 060, 163 855, 154 178, 136 636, 303 570, 302 833, 306 696, 189 972, 455 000, 135 956, 471 372, 302 389; German Offen-legungsschriften (German Published Specifications) Nos. 3 639 877, 3 712 307; Japanese Offenlegungs-schriften (Japanese Published Applications) Nos. 03 220 176, 02 207 083, 63 307 857, 63 287 764, 03 246 283, 04 9371, 03 279 359, 03 255 072, U.S. Patents 5,034,524, 4,948,798, 4,918,086, 5,039,686 and 5,034,404; PCT Applications Nos. WO 91/17 659, 91/4965; French Application No. 2 611 114; and Brazilian Application No. 88 03 621. The compounds described in these publications and their preparation are hereby expressly incorporated herein by reference.

These compounds can be advantageously represented by the general formula (I)



(I),

in which

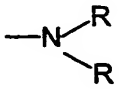
R represents, hydrogen, optionally, substituted radicals from acyl, alkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl;

A represents a monofunctional group from hydrogen, acyl, alkyl, aryl, or represents a bifunctional group which is linked to the radical Z;

E represents an electron-withdrawing radical;

X represents the radicals -CH= or =N-, it being possible for the radical -CH= instead of an H atom to be linked to the radical Z;

Z represents a monofunctional group from alkyl, -O-R, -S-R,



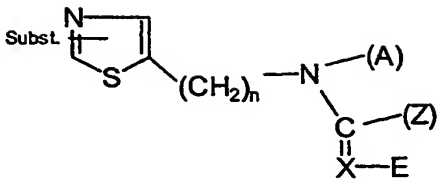
or represents a bifunctional group which is linked to the radical A or to the radical X.

trifluoromethyl; hydroxyl; halogen, preferably fluorine, chlorine, bromine and iodine, especially fluorine, chlorine and bromine; cyano; nitro; amino; monoalkyl- and dialkylamino having preferably 1 to 4, in particular 1 or 2 carbon atoms per alkyl group, such as methylamino, methyl-ethyl-amino, n- and i-propylamino and methyl-n-butylamino; carboxyl; carbalkoxy having preferably 2 to 4, in particular 2 or 3 carbon atoms, such as carbomethoxy and carboethoxy; sulpho ($-SO_3H$); alkylsulfonyl having preferably 1 to 4, in particular 1 or 2 carbon atoms, such as methylsulfonyl and ethylsulfonyl; arylsulfonyl having preferably 6 or 10 aryl carbon atoms, such as phenylsulfonyl, and also heteroarylamino and heteroarylalkylamino such as chloropyridylamino and chloropyridyl-methylamino.

A particularly preferably represents hydrogen and represents optionally substituted radicals from acyl, alkyl or aryl, which preferably have the meanings given for R. A additionally represents a bifunctional group. There may be mentioned optionally substituted alkylene having 1-4, in particular 1-2 C atoms, substituents which may be mentioned being the substituents listed earlier above, and it being possible for the alkylene groups to be interrupted by hetero atoms from the group consisting of N, O or S.

A and Z may, together with the atoms to which they are attached, form a saturated or unsaturated heterocyclic ring. The heterocyclic ring can contain a further 1 or 2 identical or different hetero atoms and/or hetero groups. Hetero atoms are preferably oxygen, sulfur or nitrogen, and hetero groups are preferably N-alkyl, where the alkyl in the N-alkyl group preferably contains 1 to 4, in particular 1 or 2 carbon atoms. As alkyl there may be mentioned methyl, ethyl, n- and i-propyl and n-, i- and t-butyl. The heterocyclic ring contains 5 to 7, preferably 5 or 6 ring members.

Examples of the heterocyclic ring which may be mentioned are imidazolidine, pyrrolidine, piperidine, piperazine, hexamethyleneimine,



(III),

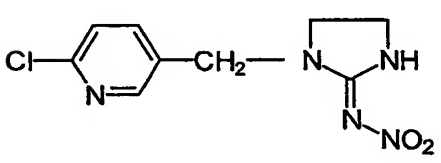
in which

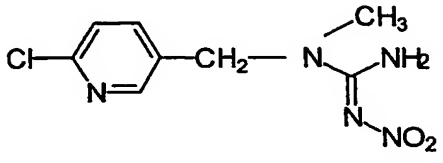
n represents 1 or 2,

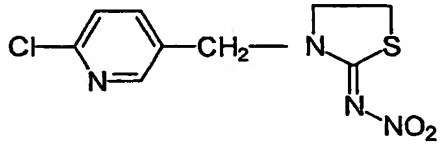
Subst. represents one of the above-listed substituents, especially halogen, very particularly chlorine,

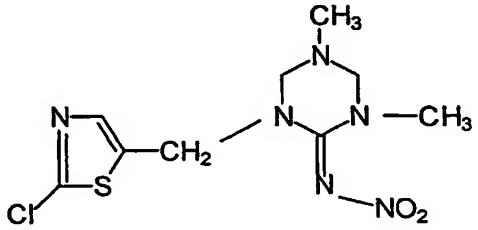
A, Z, X and E have the meanings given above,

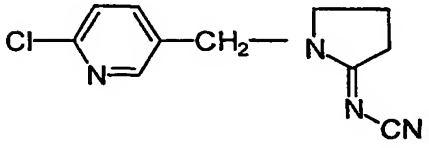
Specifically, the following compounds may be mentioned:

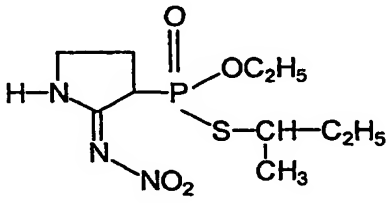


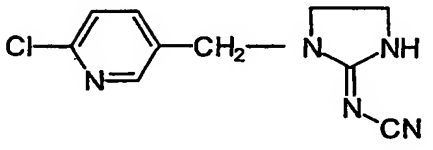


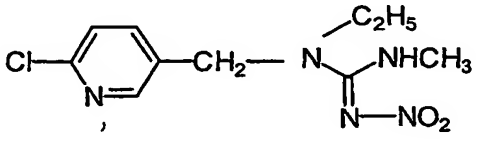


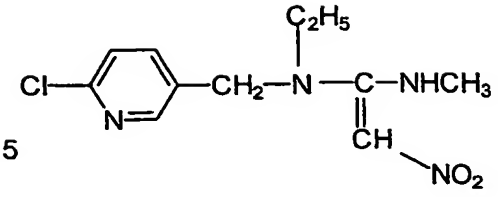


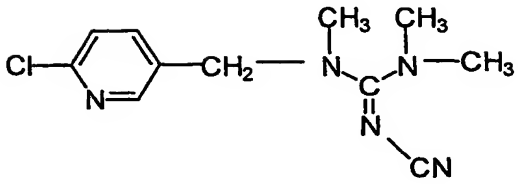


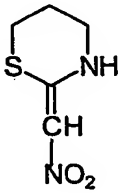


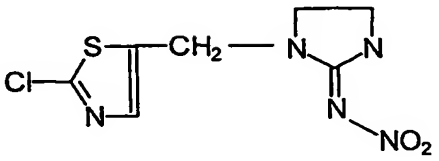


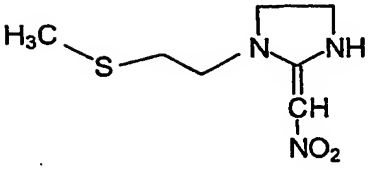


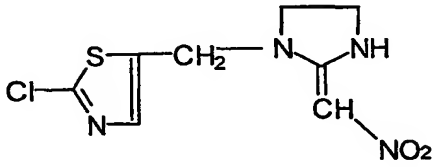


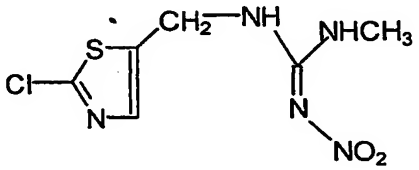












In the method of preparing the composition of the invention, the active ingredients can be combined in any convenient manner such as in an aqueous solution, suspension or emulsion or solid matrices such as ear tags or collars. Preferably, both active ingredients are soluble in one or more solvents used in the formulation. The active ingredients may be combined by mixing with extenders such as liquid solvents, pressurized liquified gases and/or solid carriers, optionally with the use of surfactants.

The concentration of the active ingredients in the composition or formulation is such as is effective to control the parasitic insects or acarids. The particular concentration would depend on the form of the formulation and the method of application. Typically, the pyrethroid can be present in

preferably from 2.5 to 12.5% by weight, particularly from 2.5 to 10.0% by weight. The sum of active compounds, solvents and auxiliaries has to be 100% by weight.

Thickeners are, for example, inorganic thickeners such as bentonites, colloidal silicic acid, aluminum monostearate, organic thickeners such as cellulose derivatives, polyvinyl alcohols, polyvinylpyrrolidones and copolymers thereof, acrylates and methacrylates.

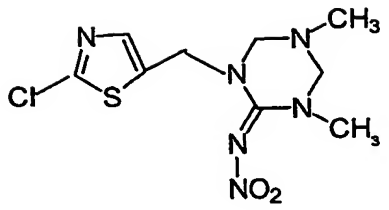
Colorants useful herein are those approved for use in drugs which may be dissolved or suspended.

Spreading agents include but are not limited to oils such as di-2-ethylhexyl adipate, isopropyl myristate, dipropylene glycol pelargonate, cyclic and acyclic silicone oils such as dimeticones and also co- and terpolymers thereof with ethylene oxide, propylene oxide and formalin, fatty acid esters, triglycerides and fatty alcohols.

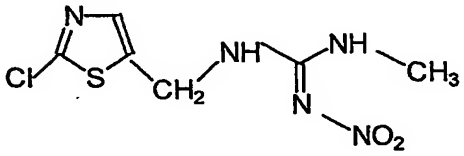
Antioxidants are, for example, sulfites or metabisulfites such as potassium metabisulfite, ascorbic acid, butylated hydroxytoluene, butylated hydroxyanisole, tocopherol. Light stabilizers are, for example, substances from the class of the benzophenones or Novantisol acid. Adhesives are, for example, polymeric thickeners, for example, cellulose derivatives, starch derivatives, polyacrylates, naturally occurring polymers such as alginates and gelatin.

Auxiliaries are also emulsifiers such as nonionic surfactants, for example polyoxyethylated castor oil, polyoxyethylated sorbitan monooleate, sorbitan monostearate, glycerol monostearate, polyoxyethyl stearate, alkylphenol polyglycol ethers; ampholytic surfactants such as disodium N-lauryl-β-iminodipropionate or lecithin; anionic surfactants such as sodium lauryl sulfate, fatty alcohol ether sulfates, mono/dialkyl-polyglycol ether orthophosphoric ester monoethanolamine salt; and cationic surfactants such as cetyltrimethylammonium chloride.

While being of low toxicity to warm-blooded species, the formulations according to the invention are suitable for the control of



Ti 435 is a chloronicotinyl derivative of the formula



In the examples which follow, the active compounds employed are [(3-phenoxyphenyl)methyl-3-92,2-dichlorovinyl)-2,2-dimethlycyclo-propanecarboxylate] having the common name permethrin and 1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine having the common name imidacloprid.

The invention is further illustrated but is not intended to be limited by the following examples in which all parts and percentages are by weight unless otherwise specified.

EXAMPLES

Example 1

The purpose of this study was to was to determine comparative flea and tick control over a 30 day interval of a combination application of a pyrethroid and a chloronicotinyl insecticide applied dermally to dogs. This combination was compared with permethrin alone, imidacloprid alone, fipronil and selamectin. The latter two compounds are present in products that currently carry claims for both tick and flea control

Thirty-six dogs were divided into six groups of 6 dogs per group. Each dog received a single topically-applied treatment of the either "Kiltix", a product available from Bayer Corporation containing 45% w/w

Table 1 Dose of Compounds Dermally Applied to Dogs

Group	Treatment	Dose	Application
1	45% Permethrin	<33 lbs = 1.5 mL >33 lbs = 2x1.5 mL	<33 lbs: 1.5 mL of solution on the back between the shoulder blades > 33 lbs : 1.5 mL between the shoulder blades + 1.5 mL on the rump at the base of the tail
2	9.1% Imidacloprid	< 10 lb = 0.4 mL 11-20 lb = 1.0 mL 21 – 55 lb = 2.5 mL >55 lb = 4.0 mL	On the back to one spot between the shoulder blades Apply evenly to 3-4 spots on the back between shoulder to base of tail
3	45% Permethrin + 9.1% Imidacloprid	Same as above for both products	Apply according to above directions but do not apply both products to the same spot
4	9.7% fipronil	<22 lbs = 0.67 mL 23-44 lbs = 1.3 mL 45-48 lbs = 2.68 mL	Apply contents of tube on the skin at one spot between the shoulder blades
5	12% Selamectin (120 mg/mL)	10.1 – 20 lb = 0.5 mL 20.1 – 40 lb = 1.0 mL 40.1 – 85 lb = 2.0 mL	Apply contents of tube on the skin at one spot between the shoulder blades
6	Control	No Treatment	

The results of this study are shown in Table 2, 3 and 4.

Table 3

COMPARATIVE EFFICACY
R. SANGUINEUS
PERCENT CONTROL

Study Day	Imidacloprid	Permethrin	Imidacloprid + Permethrin	Fipronil	Selamectin
1	15.5	72.7	76.8	96.3	-13.1
2	42.4	75.0	85.9	100	48.5
3	35.9	85.0	91.8	100	87.4
7	67.2	99.4	98.9	100	83.9
8	72.0	100	100	100	83.6
9	66.6	99.0	100	100	95.6
14	53.5	95.2	95.2	99.4	21.5
15	58.2	98.9	98.2	100	46.0
16	54.0	99.4	98.4	99.4	70.9
21	41.5	89.4	87.0	86.0	-7.0
22	18.9	91.7	91.8	100	-2.2
23	-5.3	91.5	99.0	100	8.2
28	39.1	68.6	84.6	65.3	-16.0

The following significant conclusions can be drawn from this study.

1. The combination of permethrin and imidacloprid produced a faster kill of both species of ticks (*D. variabilis* and *R. sanguineus*) than either permethrin or imidacloprid alone. The combination provided 82 to 86% killing of ticks by day 2 post application and approximately 100% killing of both species of ticks by day 3 post application. Permethrin alone required 7 days to approach a 100% killing of ticks. Selamectin required 9 days to reach only an 83% killing of *D. variabilis,* and then this compound lost its activity. Selamectin produced earlier killing of R. sanguineus (87% by day 3), however, the tick killing of selamectin decreased rapidly and was negligent by day 16 post application. Fipronil produced an early kill, similar to that of the combination of permethrin and imidacloprid.
2. The length of time that significant tick control occurred with the combination of permethrin and imidacloprid was significantly longer than that of permethrin alone, imidacloprid alone, selamectin or fipronil. The data indicate that the combination of permethrin and imidacloprid controlled 85 to 92 % of both species of ticks by 28 days post application.
3. The killing of fleas on dogs remained unaffected by the presence of permethrin in the formulation. Table 4 indicates that permethrin alone had some killing effect on fleas from day 1 through day 21 whereas imidacloprid killed essentially all of the fleas from day 1 through day 30. The combination of permethrin and imidacloprid demonstrated an equally effective killing of fleas from day 1 through day 30. Selamectin was not as effective as either imidacloprid or the combination of imidacloprid and permethrin. The latter compound required 3 days to demonstrate a significant killing of fleas and then this killing effect appeared to fall by 28 days post application. Fipronil demonstrated a rate of flea kill equal to that of imidacloprid or the combination of imidacloprid and permethrin.

WHAT IS CLAIMED IS:

1. A composition for control of parasitic insects and acarids comprising a combination of a pyrethroid and a nicotinyl compound.

2. The composition of Claim 1 wherein in the pyrethroid is in a concentration of from 0.1 to 60% by weight and the nicotinyl compound is in a concentration of 0.001 to 25% by weight, based on the overall weight of the combination.

3. The composition of Claim 1wherein the pyrethroid is permethrin.

4. The composition of Claim 1 wherein the nicotinyl compound is imidacloprid.

5. The composition of Claim 1 comprising permithrin and imidacloprid.

6. A formulation for dermal control of parasitic insects and acarids comprising the combination of Claim 1, a solvent and optionally an auxiliary.

7. A method of preparing the composition as recited in Claim 1, comprising mixing the pyrethroid and nicotinyl compound.

8. A method of preparing the formulation of Claim 6, comprising mixing the pyrethroids, the nicotinyl compound, the solvent, and optionally the auxiliary.

9. A process of treating a mammal or premise infected with insects and acarids comprising administering to the mammal or premise with the composition of Claim 1.

10. A process of treating a mammal or premise infected with insects and acarids comprising administering to the mammal or premise with the formulation of Claim 6.

INTERNATIONAL SEARCH REPORT

Interna[redacted]l Application No
PCT/US 01/44084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N53/00 //(A01N53/00,51:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS, CHEM ABS Data, CAB Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 17520 A (BAYER AG ;SIRINYAN KIRKOR (DE); DORN HUBERT (DE); KUJANEK RICHARD) 13 June 1996 (1996-06-13) page 1, line 13 -page 2, line 7 page 6, line 5 - line 17 page 10, line 17 -page 11, line 23 page 12, line 12 -page 13, line 5 page 22; example 13 ---	1,2,4, 6-10
X	EP 0 387 663 A (BAYER AG) 19 September 1990 (1990-09-19) page 2, line 26 -page 3, line 5 page 8, line 1 - line 29 ---	1-5,7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2002	31/05/2002

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Lamers, W

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INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
PCT/US 01/44084

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